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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/559,882	12/07/2005	Armin Prasch	SMB-PT164 (PC 04 246 K US	2925

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EXAMINER	
WESTERBERG, NISSA M	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/559,882	PRASCH ET AL.	
	Examiner	Art Unit	
	Nissa M. Westerberg	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 - 20* is/are pending in the application.

4a) Of the above claim(s) *10, 13, 15 - 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 - 9, 11, 12, 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed August 14, 2008, have been fully considered. The following rejections and/or objections constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 – 2nd Paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the first separate step, it is unclear what roles the "powder-wetting or dispersing device" and the "jet stream mixer" play. A jet stream mixer homogenizes and/or deaerates the dispersion in the water, but the suspending is carried out by a powder-wetting or dispersing device under at least one of deaeration and homogenization. The Examiner cannot determine if the jet stream mixer and powder-wetting/dispersing are used concomitantly or if the suspension takes place using a powder-wetting or dispersing device and then the solution produced is homogenized or deaerated by a jet stream mixer.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1 – 3, 11, 12 and 14 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Bosch et al. (US 2002/0102294).

Bosch et al. discloses spray-dried powders made by spray-drying an aqueous suspension of a nanoparticulate drug and a surface modifier to form a dry powder which consists of aggregated drug nanoparticles (¶ [0025]). As the aggregates have a size of about 1 to about 2 microns, the nanoparticulate drug (micronized particles of the effective agent) used to start the process must meet the limitation of having a grain size of 30 μm or less, as recited in claim 3 of the instant application. This aqueous dispersion can contain a dissolved diluent such as lactose or mannitol that form diluent particles that contain at least on embedded nanoparticle and surface modifier (¶ [0026]). The powders thus produced can be used in DPIs or pMDIs (dry powder inhaler or pressurized meter dose inhalers, ¶ [0007]) or reconstituted and used in nebulizers to generate aqueous dispersion have respirable droplet sizes (¶ [0027]). The product is further processed into a pharmaceutical formulation as required in claim 14.

In example 3, a ratio of 10:1 of effective agent (naproxen) to functional adjuvant (polyvinylpyrolidone, PVP) is prepared and milled to a mean particle size of 254 nm (¶ [0119]). An additional solution containing naproxen, which could be considered a functional adjuvant, is added in two separate steps as further milling and preparation for injection was carried out (¶ [0119]). The suspension was then spray dried ((¶ [0119]) and show a spherical shape (¶ [0121]) and a MMAD (mass median aerodynamic diameter) of 1.67μm (¶ [0120]). No inert starter pellets or cores are present in the machinery when the spraying process is commenced.

The product made by the steps of dissolving the diluent and other excipients in a solution in the aqueous dispersion and the product made by the steps of Instant Claim 1 in which the excipients are made into a solution that is subsequently mixed with the aqueous dispersion, are identical. The process disclosed by Bosch et al. and that of Instant Claim 1 are therefore not patentably distinct. "Selection of any order of process steps is prima facia obvious in the absence of new or unexpected results." See MPEP § 2144.04, IV.

It would be obvious to one of ordinary skill in the art to vary the order of steps because, in such a method, where the order of steps is not critical, one of ordinary skill in the art would have recognized that varying the order of steps would result in an equivalent means of carrying out the method.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1 – 3, 7 – 9, 11, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al. (US 2002/0102294) in view of Remington: The Science and Practice of Pharmacy, 20th edition (2000, p 742 – 745, 868 – 869) and Uhlemann et al. (US 4,946,654).

Bosch et al. discloses spray-dried powders made by spray-drying an aqueous suspension of a nanoparticulate drug and a surface modifier to form a dry powder which consists of aggregated drug nanoparticles (¶ [0025]). As the aggregates have a size of about 1 to about 2 microns, the nanoparticulate drug (micronized particles of the effective agent) used to start the process must meet the limitation of having a grain size of 30 μm or less. This aqueous dispersion can contain a dissolved diluent such as lactose or mannitol that form diluent particles that contain at least on embedded nanoparticle and surface modifier (¶ [0026]). The powders thus produced can be used in DPIs or pMDIs (dry powder inhaler or pressurized meter dose inhalers, ¶ [0007]) or reconstituted and used in nebulizers to generate aqueous dispersion have respirable droplet sizes (¶ [0027]).

In example 3, a ratio of 10:1 of effective agent (naproxen) to functional adjuvant (polyvinylpyrolidone, PVP) is prepared and milled to a mean particle size of 254 nm (¶ [0119]). An additional solution containing naproxen, which could be considered a functional adjuvant, is added in two separate steps as further milling and preparation for injection was carried out (¶ [0119]). The suspension was then spray dried ((¶ [0119]) and show a spherical shape (¶ [0121]) and a MMAD (mass median aerodynamic

diameter) of 1.67μm (¶ [0120]). No inert starter pellets or cores are present in the machinery when the spraying process is commenced.

The spray drier used in Bosch et al. is a top spray model (Yamato GB-22) and therefore the limitation in claim 7 as to the dispersion being injected from the bottom is not meet. Deaeration of the solution is not explicitly taught by Bosch et al. The inclusion of a sifting device with the spray drying apparatus which removes particles of a predetermined size is also not taught by Bosch et al.

Remington discloses that several different types of fluid-bed apparatus, wherein the solution is injected from the top, bottom or side can be used in the granulation process (p 868 – 869, see particularly figure 45-12). Remington also discloses that when suspensions are prepared, the fine drug particles are treated with a liquid and allowed to stand for several hours to release trapped air (deaeration; p 744, col 2, ¶ 6). The suspending agent (functional adjuvant) is dissolved or dispersed in the main portion of the external phase and allowed to stand until complete hydration takes place (p 744, col 2, ¶ 6). The wetted drug particles are added to the main portion of the dissolved suspending agent (p 744, col 2, ¶ 6).

Uhlemann et al. discloses a process for continuously preparing granules by spraying a liquid into a fluidized bed under condition in which granules of a predetermined size are formed and removed via a classifier inserted into the outflow (abstract). The growth of the particles in the fluidized starts from nuclei that are formed in the fluidized bed or particles which are already present (col 1, ln 31 – 4). This process results in no material being lost as particles which are too small remain in the fluidized

bed until they reach the desired size and particles are removed before they can become too large (col 3, ln 65 – col 4, ln 4).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to prepare the particulate compositions of Bosch et al. and to use a spray dryer in which the liquid enters the chamber of the apparatus from the bottom as opposed to the top, as such apparatuses are well-known in the art, as taught by Remington. Mixing of the particles with a liquid and allowing the particles to remain in contact with the liquid results in deaeration. If the starting solution is not homogenous when the final particles are made, the produced particles will not be homogenous, which would lead to quality control issues in that not all of the particles would contain the same amount of active ingredient. Likewise, the inclusion of a classification sifter and the use of apparatus such as that taught by Uhlemann et al. would have been obvious to one of ordinary skill in the art as this process results in a final product with a narrow size distribution and no loss of materials that are too small or too bog for use in the pharmaceutical product.

9. Claims 1 – 4, 7 – 9, 11, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al., Remington and Uhlemann et al. as applied to claims 1 – 3, 7 – 9, 11, 12 and 14 above, and further in view of Liversidge et al. (US 5,145,684).

As discussed above, Bosch et al., Remington and Uhlemann et al. disclose a method of producing particle of drug in a process in which a liquid dispersion of a drug

and functional adjuvants also dissolved in liquid are spray dried to form particles. Inert cores or seeds need not be present when the spray drying process is begun.

None of the references disclose the use of a polyoxypropylene-polyoxyethylene as a functional adjuvant.

Liversidge et al. discloses drug particles of small effective particles that exhibit increased bioavailability (abstract) of poorly soluble drug substance (col 3, ln 38 – 44) and a surface modifier (abstract). It is believed that the surface modifer alters the interactions of the fine particles (col 8, ln 21 – 30). A wide variety of compounds can be used as surface modifiers (col 4, ln 34 – 63), but particularly preferred are polyvinylpyrrolidone and PLURONIC® F68 and F 108, polyoxypropylene and polyoxyethylene copolymers (col 4, ln 64 – 67).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to replace the PVP used in the dispersions described by Bosch et al. with the functionally equivalent polyoxypropoylene and polyoxyethylene copolymers, as taught by Liversidge et al.

10. Claims 1 – 3, 5 – 9, 11, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al., Remington, Uhlemann et al. and Liversidge et al. as applied to claims 1 – 4, 7 – 9, 11, 12 and 14 above, and further in view of Appel et al. (EP 1027867).

As discussed above, Bosch et al., Remington and Uhlemann et al. discloses a method of producing particle of drug in a process in which a liquid dispersion of a drug

and functional adjuvants also dissolved in liquid are spray dried to form particles. Inert cores or seeds need not be present when the spray drying process is begun. Liversidge et al. detaches that decreasing the particle size results in increased bioavailability of the active ingredient.

None of the references disclose the use of clarithomycin as effective agent.

Appel et al. discloses spray-dried dosage forms of a solid dispersion of a drug (abstract) of sparingly water soluble drugs (¶ [0002]). The drugs can be delivered as aqueous suspensions (¶ [0013]). Among the drugs identified as belonging to this category is the macrolide antibiotic clarithomycin (p 5, ln 30).

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to use clarithomycin, taught by Appel et al. as a poorly water soluble active ingredient, as the effective agent in the process of making solid particles taught by Bosch et al., Remington and Uhlemann et al. to alter the bioavailability of this active ingredient, as taught by Liversidge et al.

Claim Objections

11. Claim 5 is objected to because of the following informalities: there appear to be numerous misspelling in active ingredients in the Markush group of this claim. For example, "nifedipine" is spelled "nifedipin" and while "clarithomycin" is recited in claim 6 and this item is spelled as "clarithomycine" in claim 5. Appropriate correction is required and not all of the apparently misspelled words have been exemplified above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nissa M. Westerberg whose telephone number is (571)270-3532. The examiner can normally be reached on M - F, 8:00 a.m. - 4 p.m. ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

NMW